Endemic Pemphigus Foliaceus (Fogo Selvagem): II. Current and Historic Epidemiologic Studies

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This paper details current and historic epidemiologic features of Fogo Selvagem (Endemic pemphigus foliaceus) in Brazil. The following features are described. a) The disease occurs in endemic fashion in regions of Brazil within the states of Goias, Mato Grosso do Sul, Parana, Sao Paulo, and Minas Gerais. It appears that the disease is spreading toward the northwest and west, involving the states of Mato Grosso, Para, Maranhao, Rondonia, Acre, and Amazonas. b) People at risk are young peasants or children of either sex or any race exposed to the local ecology in rural areas of endemic states. Although the disease has been described in urban centers, these occurrences are rare. c) Fogo Selvagem commonly appears in wild areas being colonized and disappears as these areas become urbanized. d) The majority of patients live in close proximity to rivers and within the 10–15 Km flying range of mosquitos or black flies (such as Simulium). It is hypothesized that a black fly, Simulium pruinosum may be the vector that precipitates the disease. f) There is a significant number of Fogo Selvagem in family units where multiple, genetically related individuals are affected. g) Finally, autoantibodies against lupus-associated antigens are not present in the sera of patients with Fogo Selvagem.

Clinical examination of the skin, and serologic screening for pemphigus autoantibodies are specific parameters that can be used in the search for the etiologic agents that lead to autoimmune disease of the skin. To identify and prove an etiologic agent for this well-characterized autoimmune disease would be of tremendous importance to the understanding of autoimmune skin diseases, and potentially other organ-specific autoimmune disorders. *J Invest Dermatol 92:4–12, 1989*

The term pemphigus refers to cutaneous diseases that are characterized by the development of intraepidermal blisters and/or mucosal erosions and antiepidermal autoantibodies [1–2]. Most forms of pemphigus occur sporadically throughout the world, the exception being endemic pemphigus foliaceus (Fogo Selvagem), which is seen commonly in Brazil. Fogo Selvagem is characterized by superficial cutaneous blisters and erosions (mucosal surfaces are rarely involved), and serologically by the presence of IgG autoantibodies that appear to react with components of the epidermal desmosomal cores, i.e., desmoglein I [3]. It is identical to the idiopathic form of pemphigus foliaceus seen in North America and Europe (as described originally by Cazenave). It differs from Cazenave's pemphigus foliaceus in its epidemiology, the frequency of familial cases, and the age distribution of affected individuals. A detailed clinical, histological and immunologic description of Fogo Selvagem has been published elsewhere [4].

The typical epidermal lesions of Fogo Selvagem have been reproduced in experimental animals by passive transfusion of patient's autoantibodies [5], establishing the autoimmune basis of Fogo Selvagem. However, the etiology of this and other forms of pemphigus is unknown.

Fogo Selvagem is endemic in certain regions of Brazil, where there are currently more than 15,000 registered cases. The affected population includes farmers, children, and young adults of all ethnic groups. The disease has a unique and striking epidemiology that strongly links an environmental "agent" (a black fly, genus *Simulium*) to the onset of Fogo Selvagem. This paper will compile current and historical epidemiologic data for Fogo Selvagem to estab-

Manuscript received December 28, 1987; accepted for publication February 3, 1988.

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This work was supported in part by U.S. Public Health Service Grants RO1-AR32599, RO1-AR32081, RO1-AR32490, KO4-AR01686, RO1-AR32079, and T32-AR07324 from the National Institutes of Health.

This work was presented in part at the national meeting of the Society of Investigative Dermatology, San Diego, California, May, 1987.

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Abbreviations:
IF: Immunofluorescence
nDNA: Native DNA

lish the foundations for future studies which may culminate in the identification of the etiologic agent(s) for this human autoimmune disease.

It is worth mentioning that the majority of epidemiologic studies of Fogo Selvagem reported in the literature are cumulative cases registered and collected by each investigator, in each hospital facility of that endemic state. However, the epidemiologic data thus obtained were not expressed in terms of incidence or prevalence of the disease per number of either urban or rural members of a population.

The Epidemiology of Fogo Selvagem

Endemic Regions of Fogo Selvagem in Brazil and Latin America: Although Fogo Selvagem has been reported sporadically in other South American countries such as Paraguay, Argentina, Bolivia, Peru, and Colombia, the greatest frequency is in Brazil [6]. A group of patients with a cutaneous syndrome similar to Fogo Selvagem has been described in certain areas of Colombia [7] and El Salvador [8]. It is not known if these patients represent true Fogo Selvagem or the idiopathic form of pemphigus foliaceus. It is conceivable that endemic pemphigus foliaceus may be precipitated by similar etiologic agents present in diverse regions of Latin America.

Fogo Selvagem occurs in Brazilian states located between 45° to 60° west longitude and 5° to 25° south latitude in regions with an altitude between 500–800 m (1,600–2,600 ft). Fogo Selvagem is rare at altitudes below 400 m (1,300 ft) or above 1,000 m (3,300 ft) [9–10]. The weather in endemic regions of Fogo Selvagem is subtropical and supports coffee, surgarcane, and cacao in northern regions, and corn, soybeans, and cotton in southern regions.

The majority of patients with Fogo Selvagem originate in endemic regions near either the Tocantins or Parana rivers or their tributaries. These rivers run northerly or southerly and terminate in the Atlantic Ocean. These regions are shown in Fig 1. According to recent publications, the Brazilian states with the greatest number of Fogo Selvagem patients are Goias, Mato Grosso do Sul, Parana, Sao Paulo, and Minas Gerais.

The Evolution of Fogo Selvagem in Brazil: The first mention of "pemphigus brasiliensis" was recorded by Francois Boissier de Lacroix (Sauvages) [11] in his Nosologia Methodica in reference to an observation made by a Father Bougeant, who was working as a missionary in Brazil in 1730. A later critical review of this publication

Figure 1. The Brazilian states with the largest numbers of patients with Fogo Selvagem are Goias, Mato Grosso do Sul, Sao Paulo, and Parana. The geographic distribution of patients *(black dots)* follows areas drained by tributaries of the Tocantins and Parana rivers. The number of black dots (cases) is an approximate representation of the geographic origin of individual cases. The cities of Campo Grande (Mato Grosso do Sul) and Goiania (Goias) have referral hospitals to treat Fogo Selvagem.

by Ramos e Silva [12] concluded that Sauvages was not in fact describing a case of Fogo Selvagem. In 1903, Paes-Leme [13] described the typical clinical presentation of Fogo Selvagem in the region of Mogiana of Sao Paulo in his thesis presented at the Faculdade de Medicina do Rio de Janeiro. However, presumably because of the circinate nature of the lesions, he misdiagnosed these patients as having Tinea Imbricata ("Tokelau").

Silva [14], in his study of Fogo Selvagem in the state of Bahia, mentioned that Professor A. Cerqueira described the first cases of the disease in 1900 in his Dermatology Service at the Faculty of Medicine in Bahia. However, these clinical descriptions were not published. The cases seen by Cerqueira were clinically and epidemiologically similar to those observed by Paes-Leme. These patients were natives of the state of Bahia where cacao and coffee plantations were replacing the native vegetation of the region.

During the VII Congreso Brasileiro de Medicina e Cirugia held in Belo Horizonte in April 1912, Aleixo [15] reported new cases of Fogo Selvagem in patients from the state of Minas Gerais, and Gualberto [16] showed several cases in adults and children from the region of Franca in the state of Sao Paulo. In the following years, the number of cases of Fogo Selvagem continued to increase in Minas Gerais, which enabled Orsini de Castro to document 107 patients by 1927 [17].

From 1930 to 1940, an increased number of patients with Fogo Selvagem were reported in the states of Minas Gerais and Sao Paulo by several investigators. A localized form of the disease was identified and presented as a Senear-Usher-like syndrome by Ramos e Silva & Peryassu [18] during the Annual Meeting of the Sociedade Brasileira de Dermatologia held in 1938.

Because the number of cases in the state of Sao Paulo increased remarkably during the 30's, the government of Sao Paulo created a hospital dedicated to treat and rehabilitate patients with Fogo Selvagem [9]. The Adhemar de Barros Hospital officially opened for patients on September 17, 1938. The hospital became the major center for treatment of Fogo Selvagem patients in Brazil and the most advanced facility for clinical and basic research of the disease. At the apogee this hospital housed approximately 300–400 inpatients. Several renowned investigators worked in this facility from its inception until recently. We find J.P. Vieira, J. Aranha-Campos, C.A. Leme, U.L. Torres, N. Proenca, R. Martins-Castro, and M. Macca, among others. Several classic clinical and epidemiological studies of Fogo Selvagem has been published by the group of the Adhemar de Barros [9,19–23].

The last 30 years have witnessed the spread of Fogo Selvagem from Bahia, and Minas Gerais toward the northwest, encompassing the states of Maranhao, Goias, and Mato Grosso, and southwest from Sao Paulo to the states of Parana and Mato Grosso do Sul. New hospitals for Fogo Selvagem patients have been opened in Goiania (Goias), and Campo Grande (Mato Groso do Sul). This development allowed Auad [10] to study and describe 2,663 cases of Fogo Selvagem registered in the hospital for pemphigus in Goiania (Goias), between 1952 and 1970. In 1970, at the Annual Meeting of the Sociedade Brasileira de Dermatologia in Goiania, it was estimated that there were at least 10,000 known cases of Fogo Selvagem in the endemic states of Brazil. Recently, Minelli [24] reported 632 cases of Fogo Selvagem from the north-central regions of Parana from 1941 to 1980, and Empinotti [25] collected data from 183 cases in the period 1976–1987 in western Parana.

There are several reports of an increased number of new cases of Fogo Selvagem in Brasilia, the newly developed capital of Brazil [10]. Brasilia was constructed in the sparsely inhabited lands of the southeastern region of the state of Goias. In recent years, there has been an increasing number of settlements in the states of Amazonas, Rondonia and Acre. Fogo Selvagem, once unknown in those regions, has now become prevalent, even among native Indians [26].

In summary, it was the consensus among the members of "The Cooperative Group on Fogo Selvagem Research" (the authors of this paper) at the second meeting held in Goiania on September 8, 1987, that total number of current cases of Fogo Selvagem in Brazil is approximately 15,000.

Table I. Frequency of Fogo Selvagem — Hospital do Penfigo Goiania, Goias, Brazil[a]

Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total
1980	16	9	11	9	9	11	6	10	10	13	9	12	125
1981	6	8	12	9	14	12	7	8	6	13	8	3	106
1982	5	11	11	11	11	8	7	11	8	10	11	8	112
1983	9	4	16	18	9	7	12	9	10	4	8	9	115
1984	10	10	13	11	16	8	5	7	13	18	6	3	120
1985	12	7	10	10	6	6	8	15	19	10	6	8	117

[a] Diaz, LA: Data collected from records of the Hospital do Penfigo, Goiania, Goias, Brazil, February, 1986.

Fogo Selvagem in the state of Goias: The state of Goias, with a total area of 642,092 square kilometers, is located in the north-central region of Brazil. Two major rivers flank the state: in the west, the Araguaia is the major tributary of the Tocantins River, which continues toward the Atlantic. In regions where Fogo Selvagem is seen the weather is subtropical. The state capital, Goiania, is located in the south-central region of Goias. One-fourth of the state's population of 4,441,482 (derived from a 1985 census) lives in Goiania, where the hospital for pemphigus is located. The economy of the state is based on agriculture, livestock, and the mining of minerals and precious stones.

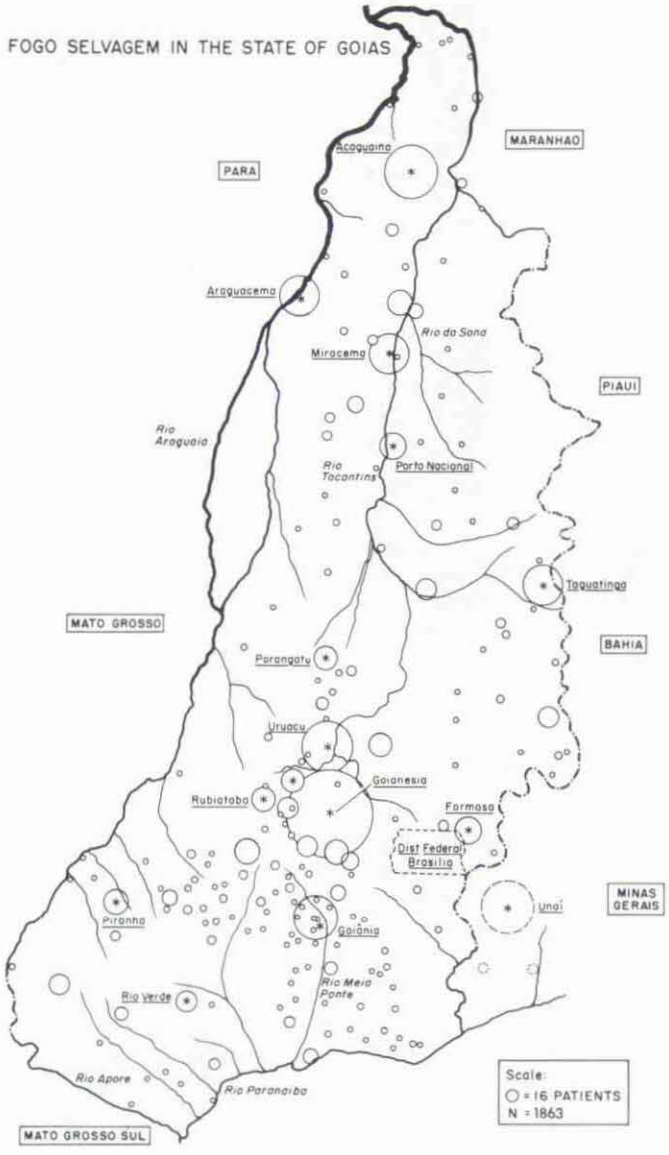

Figure 2. Distribution of Fogo Selvagem patients as reported by Auad [10] in the state of Goias in 1971. Patients are registered on the map according to the municipio (county) from where they originated. The diameters of the *open circles* represent a certain number of patients, according with the scale shown at the bottom of the figure. This figure is a modified version of the original publication of Auad [10] representing the distribution of 1863 patients out of a total of 2,663 reported by this author.

In 1970, Auad [10] reported the single largest series of patients with Fogo Selvagem, seen at the hospital for pemphigus in Goiania. In the period 1952–1970, he collected data from 2,663 cases of Fogo Selvagem (average: 148 cases/year) and 37 cases of Pemphigus Vulgaris. The ratio of cases of Fogo Selvagem to cases of Pemphigus Vulgaris was 71:1. From 1970 to December 1985, the number of new Fogo Selvagem patients registered in this hospital increased by 2,380, bringing the total number to 5,043 cases during the period from 1952–1985 [27]. Table I shows the frequency of new cases of Fogo Selvagem, in cases per month seen at the Hospital do Penfigo in Goiania, January 1980–December 1985. The average daily census of hospitalized patients in this facility was between 20 and 30.

The following important conclusions were derived from Auad's studies. a) Fogo Selvagem is a disease of young adults and children. b) Fogo Selvagem is a disease of rural people, i.e., more than 90% of his patients were peasants, laborers, and their families. c) There was no remarkable sex or race distribution among these cases. d) It was common to find cases where multiple members of the same household were affected. The geographic distribution of cases in the state of Goias is seen in Fig 2. It is clear that the majority of cases originated from areas neighboring the Tocantins River and its tributaries. Cases were clustered in the central areas of the state.

Fogo Selvagem in the state of Parana: Parana is bordered by the state of Sao Paulo to the north, Santa Catarina to the south, the state of Mato Grosso do Sul and Paraguay to the west, and the Atlantic Ocean on the east. Parana has a total area of 199,554 square kilometers and the Paranapanema River forms its northern boundary. This river runs from east to west and merges with the Parana River in western Parana. The Parana River and the Itaipu Reservoir form the western border of the state. One-eighth of the state population of 8,067,161 lives in Curitiba, the state capital. Parana is an agricultural state; the major crops are coffee, wheat, soybeans, and corn.

It seems that after the Brazilian and Paraguayan governments built the Itaipu reservoir and hydroelectric plant, which dammed the waters of the Parana River to produce the world's largest dam, with a man-made lake so large that the landlocked state of Paraguay maintains a navy to patrol it, the weather conditions in the western regions of the state of Parana changed. This may have influenced the appearence of new cases of Fogo Selvagem in this area, as recently reported by Empinotti [25].

From 1941 to 1950, Fogo Selvagem was described sporadically in the state of Parana [28], although, in the following years the number of cases detected has gradually increased. In 1976, Minelli [24] reported a series of 506 cases of Fogo Selvagem in the state of Parana in the period 1941–1973. A recent study by the same author [29] extended these observations to include Fogo Selvagem patients seen in the years following. This investigator reported a total of 632 patients in the state of Parana in the period 1940–1980. As seen in Fig 3, the majority of patients were clustered in northern regions of the state immediately south of the Paranapanema River, where the

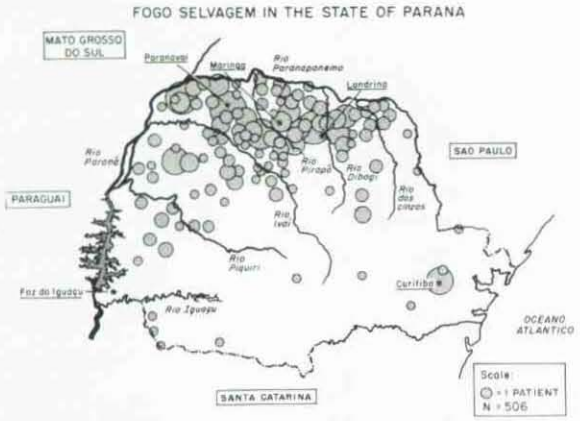

Figure 3. Distribution of Fogo Selvagem patients as reported by Minelli [24] in the state of Parana, in 1976. Patients are registered on the map according to the municipio from where they originated. The diameters of the *open circles* represent a certain number of patients, according with the scale shown at the bottom of the figure. This figure is a modified version of the original publication of Minelli [24] representing the distribution of 506 patients reported by this author.

weather is hot and humid. Fewer cases were observed in southern regions of the state, which have different ecologic characteristics than the northern areas.

Minelli's principle findings can be summarized as follows. a) Fogo Selvagem in Parana affects young individuals. b) Over 85% of the patients were peasants or their families lived in rural areas and were involved with agricultural or outdoor activities. c) There were eleven families with more than one case of Fogo Selvagem, totalling 24 patients, all in genetically linked household members.

In a recent study, Empinotti et al [25] reported 191 cases of pemphigus from western Parana. One hundred eighty-one of these cases were Fogo Selvagem and 8 were Pemphigus Vulgaris. The majority of cases were clustered in the municipios of Toledo and Cascavel. This group of patients (90% of the cases) consisted of peasants from rural areas working in agriculture or outdoor labor.

The Frequency of Fogo Selvagem in Sao Paulo is decreasing: The state of Sao Paulo, with an area of 247,898 square kilometers is located in the east-central region of Brazil. It is bordered by the Atlantic Ocean to the east, the state of Mato Grosso do Sul to the west, Minas Gerais to the north, and Parana to the south. The estimated population of Sao Paulo in 1985 was 29.5 million. The city of Sao Paulo is the state capital and has an estimated population of 10 million.

For years, the state of Sao Paulo has been the leader in the agricultural and technological growth of Brazil. Coffee, sugarcane, corn, beans, and other agricultural products have been plentifully harvested for decades. Recently, Sao Paulo has become the home of many industries, such as aircraft and automobile manufacturing, and the production of heavy agricultural equipment. Progress in agricultural methods and advances in technology have made Sao Paulo play a major role in the overall economy of Brazil. As a consequence, poor people from underdeveloped states have migrated to Sao Paulo, causing a population explosion, especially in the capital and other cities in the interior of the state. The growth and development of the state of Sao Paulo in the last 80 years has led to many social problems.

It has been noticed by several Brazilian investigators that Fogo Selvagem is currently spreading out of the state of Sao Paulo toward the north, west, and south. The disease was commonly seen in the state of Sao Paulo in the 1930's and 1940's, forcing the government to build the Adhemar de Barros Hospital to treat these patients [9,19–23], but during the 50's, 60's, 70's, and 80's, the number of cases of Fogo Selvagem seen at the Adhemar de Barros Hospital has

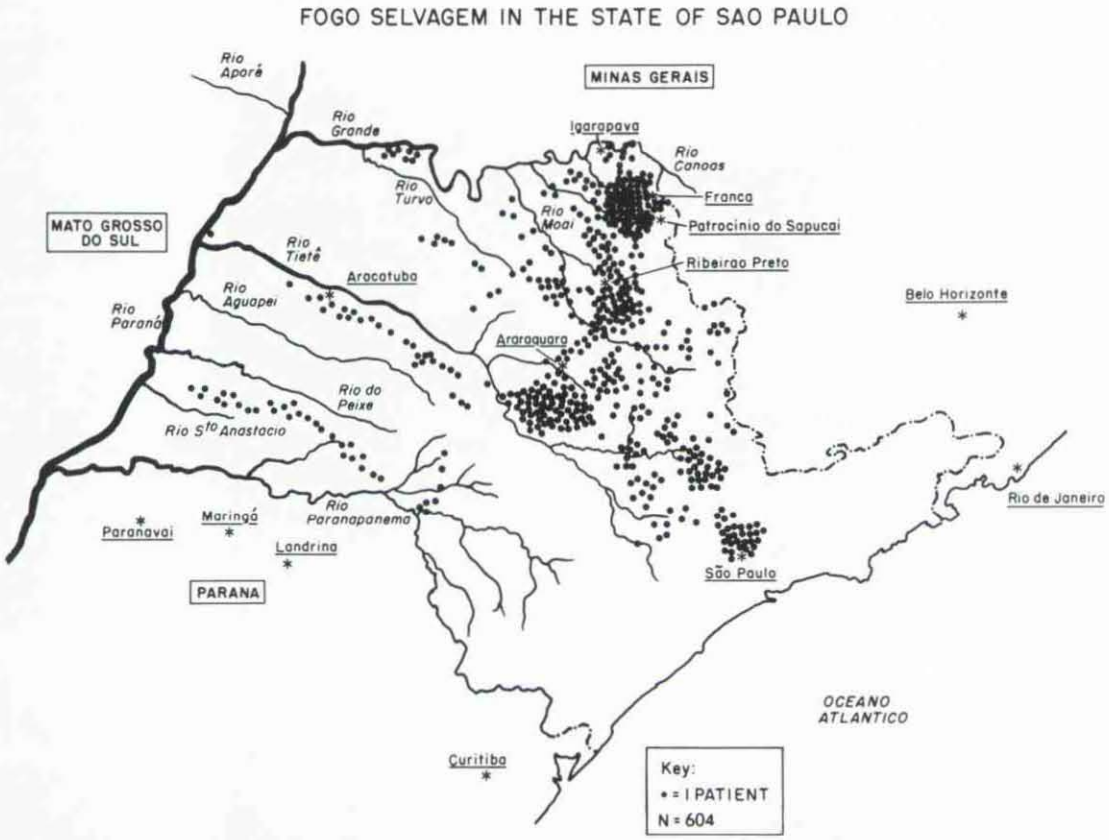

Figure 4. Distribution of Fogo Selvagem patients as reported by Aranha-Campos [9] in the state of Sao Paulo in 1942. Patients are represented by *black dots* according to their municipio of origin. This figure is a modified version of the original publication of Aranha-Campos [9] representing the distribution of 604 patients reported by this author.

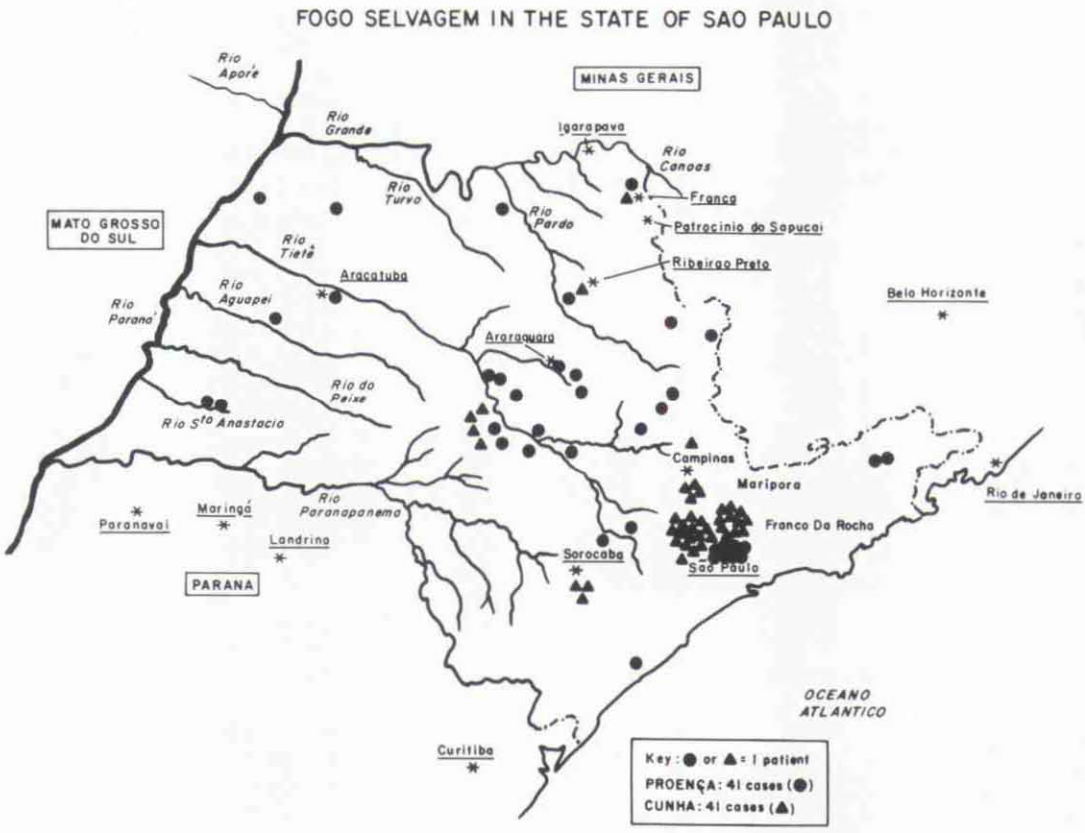

Figure 5. Distribution of Fogo Selvagem patients as reported by Proenca [32] in 1974 *(black circles)* and Cunha [31] in 1987 *(triangles)* in the state of Sao Paulo. Patients are registered on the map according to their municipio of origin. Comparison of the cases reported by Proenca and Cunha with those gathered by Aranha-Campos in 1942 (Fig 4) demonstrates the changing occurrence of Fogo Selvagem in the state of Sao Paulo in the last 40 years.

been gradually decreasing. For example, during the last few years, it has been unusual to find more than five hospitalized patients in a single day [31]. Presently, this hospital is used to treat tropical diseases other than pemphigus.

Several papers published in the 1930's and 1940's by Vieira [19] and Aranha-Campos [9] described epidemiologic features of Fogo Selvagem in the state of Sao Paulo. Figure 4 shows the geographic distribution of individual patients according to their municipio of origin as reported by Aranha-Campos in 1942. The 604 Fogo Selvagem patients originated from highly endemic municipios (Franca, Bocaina, Riberao Preto, etc.) located in proximity to rivers.

Two recent studies of the epidemiology of Fogo Selvagem in the state of Sao Paulo, by Proenca [32] and Cunha [31], demonstrate the decrease in the frequency of the disease that has been observed in the last 40 years. In 1973, Proenca [32] surveyed dermatologists working in universities, hospitals, and health clinics across the state of Sao Paulo and found only 41 cases of Fogo Selvagem. Recently, Cunha et al [31] have collected 41 cases of Fogo Selvagem seen in the area of Jundai, Franco da Rocha, and Mairipora located 60–100 km northwest of the city of Sao Paulo. According to Cunha, this cluster of Fogo Selvagem patients represents the last endemic focus of the disease in the state of Sao Paulo. The patient data reported by Proenca [32] and Cunha [31] is shown in Fig 5. The remarkable difference between the number and distribution of cases reported by Aranha-Campos and Proenca and Cunha are clearly seen by comparing Figs 4 and 5. In addition, Table II shows the decrease in the number of cases reported by these investigators in endemic counties of the state of Sao Paulo.

It is likely that the decrease in the frequency of Fogo Selvagem in the state of Sao Paulo is related to the advance in technology and changes in the ecology and personal habits of individuals. Therefore, exposure to potential etiologic factors, which may have precipitated Fogo Selvagem in the past but currently are no longer present, may have altered the local epidemiology of the disease. It is also possible, but unlikely, that patients are seen and treated early in the course of the disease and consequently are not reported to health authorities. It is important to stress that despite exponential growth of the population in the state of Sao Paulo in the last few decades, the reported frequency in Fogo Selvagem in this state has decreased dramatically.

Fogo Selvagem in other Brazilian states: The prevalence and incidence of Fogo Selvagem in other states is not well documented. A small hospital facility exists in the city of Uberaba, located in the southern region of Minas Gerais. It is supported by private donations, and Fogo Selvagem patients are treated without medical supervision. The number of patients this small hospital admitted per year and those admitted to facilities in other cities in the state of Minas Gerais

Table II. Comparison of Reported Cases of Fogo Selvagem in Endemic Municipios in the State of Sao Paulo

Municipios (Counties)	Aranha (1942)	Proenca (1973–74)	Cunha (1982–87)
Araraquara	10	2	0
Campinas	19	0	1
Bocaina	18	1	0
Dois Corregos	25	1	1
Franca	71	0	1
Jau	23	0	3
R. Preto	28	0	1
S. Carlos	21	0	0
F-Rocha/Jundai Mairipora Sao Paulo	36	6	34
Other	353	31	0
Total	604	41	41

is not yet available. It is known that Fogo Selvagem is also seen in the states of Bahia, Maranhao, Piaui, and Para, because patients from these regions are treated in the hospital for pemphigus in Goiania. In 1971, Silva and Brito [33] reported 15 cases of Fogo Selvagem from the state of Para. Para borders the state of Amazonas to the west. In 1975, Talhari et al [26] reported 10 cases of Fogo Selvagem from the state of Amazonas treated at the University Hospital of the Faculdade de Medicina do Amazonas.

In 1975, Mansur et al [34] reported 30 patients with Fogo Selvagem and 14 cases of Pemphigus Vulgaris seen at the Hospital Universitario do Rio de Janeiro in the period 1959–1975. Approximately 80% of all patients seen in this hospital come from metropolitan Rio, 20% come from the interior of the state of Rio de Janeiro. They found that all 14 cases of Pemphigus Vulgaris originated from metropolitan Rio and all Fogo Selvagem patients came from the interior of the state. The majority of Fogo Selvagem patients were farmers or their relatives.

Finally, the state of Mato Grosso do Sul (population 1,611,106), located in the southwestern part of Brazil, is another endemic focus of Fogo Selvagem. The Hospital Adventista do Penfigo is located in the state capital, Campo Grande (population 386,520). It officially opened on November 9, 1952 and has been treating patients with Fogo Selvagem from the state of Mato Grosso do Sul. It also functions as a referral center for patients from neighboring states, i.e., Parana, Mato Grosso, Rondonia, Acre, and Paraguay. It is thought that the number of cases seen in this hospital may be higher than the number treated at the hospital for Fogo Selvagem in Goiania; however, precise data are not available. It is well documented that the daily census of hospitalized patients in this facility is approximately equal to that of the hospital of Goiania, between 20 and 30 cases per day.

The hospital for pemphigus in Campo Grande popularized the local treatment of Fogo Selvagem with "Jamarsan," a tar paste developed by the pharmacist Isidoro Jamar [35]. The neighborhood of the city of Campo Grande where the Fogo Selvagem hospital is located is named "penfigo," the Portuguese name for pemphigus. City buses in Campo Grande carry the label "penfigo" in their itinerary if they go to the neighborhood of "penfigo."

Relevant Data Concerning the Etiology of Fogo Selvagem

The Patient and his Environment ("pemphigus country"): The sum of the epidemiologic data, gathered since the early descriptions of Fogo Selvagem, emphasizes the relationship of Fogo Selvagem to the daily activities and geographic origin of the patient. It has been noted that Fogo Selvagem most frequently affects people living in and colonizing native areas, and the frequency of new cases gradually decreases as the area becomes urbanized. It is therefore reasonable that study of the areas where these patients spend their lives may help to disclose the etiology of Fogo Selvagem. In the following sections we will attempt to briefly describe the agricultural farms and health care systems within the political structure of the Brazilian states, the patient with Fogo Selvagem and his family, and the local surroundings of the patients.

Politically, each state in Brazil is divided in municipios (counties). Each municipio has an urban area and a rural area. The rural area includes private properties named "fazendas" or farms. The owner of the "fazenda" may hire up to several hundred peasants to take care of the routine agricultural tasks. Some of them may be temporary workers hired to perform agricultural activities for only a short time. Technology applied to agricultural activities varies: some are modern, mechanized facilities, others cultivate the land using rudimentary methods. The health care of members of the "fazenda" depends on the facilities provided by the state or federal government. Local outpatient clinics (Unidade de Saude) are found in the major city of each municipio. In addition, patients who can afford private physicians or clinics may find them in the major cities. State hospitals offer facilities for local patients or patients referred from other states. The hospitals for pemphigus are located in large modern cities such as Goiania, Campo Grande, and Sao Paulo. They gather patients from large referral areas within the state. On occasion, these patients are flown by plane from long distances. In general, patients developing Fogo Selvagem in the "fazenda" will first be evaluated in the local outpatient clinic and then transferred to the state hospital if necessary. Drugs to treat the disease are usually provided without cost to the patient. Patients undergoing treatment for Fogo Selvagem can remain in the hospital for several weeks and then return home to the "fazenda." Patients in clinical remission are seen periodically in the outpatient clinics.

The patient afflicted by Fogo Selvagem is usually a peasant (or a member of the family) who farms in the fields or works outdoors. They are usually young adults or children. There is no reported sex or race predisposition for the development of Fogo Selvagem [9–10,19,24–25]. In general, poor peasant families move to a farm and live in rustic houses located near rivers or creeks (Fig 6). Some of the rivers or streams are infested by a variety of insects, because they contain shallow waters and rock beds, which are breeding areas for Simulium flies (black fly, also known as "borrachudo" in Portuguese), implicated as a possible etiologic agent of Fogo Selvagem. The number of new cases of Fogo Selvagem is greatest at the end of the rainy season and least during the dry summer, suggesting that insect multiplication and increase in the number of Fogo Selvagem patients are related phenomena [9–10,19]. The houses of these patients are usually located within 10 to 15 km of rivers or creeks, again suggesting transmission of the disease by a flying insect [9]. It is also known that in areas where there are prevailing winds, the zone of affected individuals shifts downwind from the body of water or river found in the endemic focus.

It is interesting that *Simulium pruinosum* is found inland, in endemic areas of Fogo Selvagem. A different species, *Simulim pertinax,* is found along the Brazilian coast where the frequency of Fogo Selvagem is extremely rare, suggesting that if this insect is the vector, there may be species specificity. Aranha-Campos [9] recounts the history of the owner of a "fazenda" named Fazenda Cocheira, located in a highly endemic region of the Municipio de Franca in the state of Sao Paulo, where many of the local peasants had contracted Fogo Selvagem. In this "fazenda," peasants and their relatives were constantly bitten by black flies ("borrachudos") and this was linked in their own explanations to the appearance of Fogo Selvagem. The owner of such fazenda brought a flock of canaries known to feed on flies and set them free. Within a short time, the birds multiplied and both the population of black flies and the number of people developing Fogo Selvagem decreased remarkably. These observations continue to implicate the arthropod *Simulium pruinosum* as the potential vector for the disease. Whether or

Figure 6. This photo shows typical "pemphigus country," the housing and the surroundings of patients with Fogo Selvagem. The countryside is subtropical, with agriculture involving soybeans, corn, and cotton. Most houses are located in proximity to rivers or creeks heavily infested with black flies ("borrachudos") and other blood-sucking insects. Domestic pets, rodents, and other animals are also found in these houses.

not the black flies are indeed involved in the etiology of Fogo Selvagem remains to be determined. It is conceivable that they may act as vectors of an "infectious" agent or be the carriers of sensitizing antigenic substances such as the insect saliva.

To complete the description of the "pemphigus country," we must include in this description other potential sources of antigens to which the patients are in close daily contact. For instance, it is common among these peasants to raise chickens, hogs, cows, and horses and to have a variety of pets such as dogs, cats, and birds. It is also common that these houses harbor rodents and other small wild animals. In some areas, other insects known to be vectors of disease such as Reduviid bugs are present, and there are usually many holes in the roofs and floors of these houses to allow entrance of such insects. Outbreaks of hepatitis A are frequent, and many communicable diseases that could be controlled simply by improving housing and hygiene are prevalent.

The daily activities of a family include agriculture, care of livestock, and home chores. Wives and children remain at home to perform routine chores, i.e., cooking, caring for small animals, or washing laundry in nearby rivers or streams. However, a great number of wives help their husbands in farming activities. The peasant and his family usually have a common bedroom and wear light clothes appropriate for the weather. The personal hygiene among these people is poor, and a diet consisting of high carbohydrate and low protein intake is common.

Fogo Selvagem is a disease of young adults and children: A repeated finding in most of the published epidemiological studies on Fogo Selvagem is the occurrence of the disease in young adults and children (Fig 7). Of the 107 cases from Minas Gerais reported by Orsini de Castro in 1927, 20% of the patients were below the age of 14, and 67% were under the age of 30 [17]. Aranha-Campos [9], in his series of 604 cases from Sao Paulo reported in 1942, found 26.4% of the patients under 14 years of age. Of 2,663 patients reported by Auad [10], in Goias in 1970, 61.5% were individuals between 10 and 40 years of age and 5.6% of the total cluster were children under 10 years of age. The youngest patient in this study was an 8-month-old child. In 1976, Proenca and Ribeiro [36] collected 464 cases from a survey of Brazilian dermatologists and found that 40% of the patients were between the ages of 15 and 30; 15.5% of the patients were under the age of 14. Twenty-eight percent of the patients in Minelli's series of 632 cases from the state of Parana [29] were between the ages of 20 and 30 and 10.7% were children under the age of 14. Gontijo's studies [37] showed that out of a total of 7,528 cases seen at the Adhemar de Barros Hospital in Sao Paulo and the Hospital Adventista de Penfigo in Mato Grosso do Sul, there were 754 cases (10%) of Fogo Selvagem in children under 14 years of age. Eighty-four percent of these children were from families living in rural areas of the states. Recently, Castro and Takahashi [38] reported 21 children under 14 years of age seen at the Department of Dermatology, Universidade de Sao Paulo, between 1962 and 1984, and showed the favorable resolution of the disease when treated with steroids. Finally, Empinotti's series of 181 cases contained 108 patients in the age range 10–40 (61%) of which 28% were between the ages of 20 and 30, and 8 children were under the age of 14 [25].

Fogo Selvagem may affect several genetically-related members of a family: Cazenave's pemphigus foliaceus and Fogo Selvagem can be differentiated by their epidemiology by the difference in age groups affected and the high frequency of familial cases in Fogo Selvagem [8] (Fig 8).

Aranha-Campos's series of 604 patients from Sao Paulo included 161 cases of Fogo Selvagem in which there was more than one family member affected [9]. In 443 families studied, there was a single case of Fogo Selvagem (n:443 cases); in 59 families there were two cases each (n:118 cases); in seven families there were three cases (n:21 cases); in three families, there were 4 cases (n:12 cases); and in two families, there were a remarkable five cases in each (n:10 cases). Of the 161 cases of Fogo Selvagem originating from families with more than one case, 110 were women and 51 men; 116 were adults and 45 children. It is particularly significant that the majority of the 161 cases were found in genetically-related members of these families (i.e., parent–child, siblings, as opposed to husband–wife).

Auad [10] reported the occurrence of 485 cases of Fogo Selvagem in 201 families, accounting for 18% of the total number of patients in his series (n:2,663). In 30 of these families, the disease affected a brother and sister; in 18 it affected a mother and her son; in 17 families the disease occurred in sisters; and in 16 in brothers. In 187 families (93%) Fogo Selvagem occurred in genetically related members of the family, whereas there were only 14 families (6.9%) in which Fogo Selvagem was seen in genetically unrelated members. Minelli's studies (24) included 11 families in which more than one genetically related member was stricken by Fogo Selvagem, accounting for 24 cases out of 506 included in the study. Proenca and Ribeiro [36] reported 55 cases out of a series of 464 patients originating from families in which there was more than one member affected by Fogo Selvagem.

Figure 7. This figure shows children with Fogo Selvagem hospitalized in the pemphigus hospital of the city of Goiania, Goias. One of the distinctive epidemiologic features of Fogo Selvagem is the common occurrence of the disease in young individuals and children. The disease responds favorably in some patients to systemic steroids. In some cases, however, the disease runs a chronic course and the incidence of steroid-side effects is very high. This is shown in one of the patients in this figure.

Figure 8. This woman had Fogo Selvagem throughout her pregnancy, with chronic lesions on the malar area and trunk. Her serum titer for pemphigus antibodies was 1 : 320. She delivered a normal child, free of cutaneous lesions. This is typical of Fogo Selvagem where neonatal pemphigus has never been reported to occur. By contrast, pemphigus neonatorum has been described several times in pemphigus vulgaris. Two brothers of this patient also have Fogo Selvagem, one in remission and the other with active disease.

Seroepidemiology of Fogo Selvagem: We have recently evaluated the sera of 196 patients: consanguineous relatives including parents, siblings, offspring, and second-degree relatives of the patients (n:138), cohabitants (n:13), normal individuals from endemic areas (n:38), and normal donors from nonendemic, urban areas (n:44). The serum samples were obtained from patients seen in hospitals located in the cities of Sao Paulo, Campo Grande, Goiania, and Brasilia. The sera were tested by a newly standardized indirect immunofluorescence (IF) procedure with normal human neonatal foreskin substrate and calcium supplemented buffer to detect pemphigus autoantibodies [39]. These sera were also tested for common lupus-associated antigens (ANA on Hep-2 cells, anti nDNA on Crithidia luciliae, Sm, nRNP, Ro/SSA, and La/SSB).

Contrary to a previous study [40], we found pemphigus autoantibodies only in the sera of patients with the disease. Differences in IF procedures applied by our group and others may explain this finding. Furthermore, there was a gross but consistent and reproducible correlation between the autoantibody titer and the extent and activity of the disease [41]. Localized forms of Fogo Selvagem showed low titers of antiepidermal autoantibodies, whereas the majority of patients with active and generalized disease showed high titers. Autoantibodies against lupus-associated antigens were not present in any of the serum samples tested.

These studies demonstrate that pemphigus autoantibodies tested by the above technique are sensitive, specific, and reliable markers of disease. Therefore, the clinical presentation of Fogo Selvagem and the detection of pemphigus autoantibodies are two relevant disease-specific parameters applicable to the identification of environmental factors triggering autoantibody formation in these patients. Prospective epidemiologic studies are currently underway in Fogo Selvagem endemic areas.

Incubation Time, Spreading, and Spontaneous Remission of Fogo Selvagem: It must be stressed that, although familial frequency of the disease is an important feature of Fogo Selvagem, this finding does not imply that the disease is contagious, because hospital workers and close contacts are not affected by the disease [6,19,20]. The disease has never been documented or even suspected of being spread by blood products or bodily fluids. The frequency of Fogo Selvagem in multiple household genetically related members of a family suggests a genetic predisposition of certain individuals to develop autoimmune disease upon exposure to environmental agent(s).

To investigate the potential role of environmental factors on the etiology of Fogo Selvagem the following groups are being studied: individuals developing the disease while living in the endemic area, individuals developing the disease after they moved out of the endemic area, and finally those individuals from nonendemic areas developing Fogo Selvagem after they arrive in the endemic area.

An interesting observation made by Mansur et al [34] in his series of 30 cases, was the existence of Fogo Selvagem in a brother and sister, in whom the disease started within a 1-month interval. Both patients were peasants from rural areas. In our recent field trips to the state of Sao Paulo we identified a family with two brothers and one sister with Fogo Selvagem in the outskirts of the city of Votorantim (Fig 8). The oldest brother was 25 years old, and Fogo Selvagem was diagnosed at the age of 15. He is currently in clinical and serologic remission. His 23-year-old sister developed Fogo Selvagem at age of 14, has had multiple hospitalizations, and currently has active cutaneous lesions, and a pemphigus antibody titer in her serum of 1:160. A younger 21-year-old brother with Fogo Selvagem of 8-years duration is in partial remission, showing skin lesions and a pemphigus antibody titer of 1:320. This family consists of 9 members who lived in a small fazenda until 1976, when they moved to the city of Votorantim. Interestingly, three of the eight brothers born on the farm developed Fogo Selvagem. The oldest patient developed the disease 1 year after moving from the farm, his sister, 2 years later, and the youngest brother, 3 years after the move.

It is also known that people moving from nonendemic areas or from a city to an endemic rural area may develop Fogo Selvagem within 6 to 12 months after arrival. The majority of these "transplanted" patients share the same ecologic systems as the local people. We have documented two interesting cases that may show this. The first was a prospector who moved to Cafelandia in the state of Goias to work in a riverbank heavily infested with black flies. The second was a teacher who moved to work in a rural school of Araguaina, an endemic municipio in the state of Goias. Both individuals developed generalized Fogo Selvagem 6 months after arriving in the endemic area.

Spontaneous remission of Fogo Selvagem had been photographically documented in a few cases before the use of steroids [9,19,20]. According to Vieira [19], spontaneous remission of the disease was expected in approximately 20% of all cases, observed in both localized and generalized forms of the disease. Aranha-Campos [9] calculated that about 7% of the generalized cases of Fogo Selvagem enter into remission (40 out of 604 patients included in his series). A classic sample of spontaneous remission of generalized Fogo Selvagem occurred in the wife of a Seventh-Day Adventist priest and was the subject of a popular book [42]. We examined this patient some 40 years after her clinical remission and found her to be in good health, and her serum was negative for pemphigus autoantibodies. This patient was treated with "Jamarsan," which was in use before steroids. After her recovery, she had more children, all in good health.

Finally, it has also been noted by Brazilian dermatologists that after treatment, Fogo Selvagem remains in remission if the patients move to the city. However, relapses usually occur if patients return to live in endemic areas, despite being under continuous treatment. If they return to the city for treatment, their disease is easy to control again. This would seem to indicate that a repeated environmental exposure predisposes to the disease.

Concluding Remarks In summary, the significant epidemiologic finding of Fogo Selvagem are as follows. a) The disease occurs in endemic fashion in regions of Brazil within the states of Goias, Mato Grosso do Sul, Parana, Sao Paulo, and Minas Gerais. It appears that the disease is spreading toward the northwest and west, involving the states of Mato Grosso, Para, Maranhao, Rondonia, Acre, and Amazonas. b) People at risk are young peasants or children of either sex or any race exposed to the local ecology in rural areas of endemic states. Although the disease has been described in urban centers, these occurrences are rare. c) Fogo Selvagem commonly appears in wild areas being colonized and disappears as these areas become urbanized. d) The majority of patients live in close proximity to rivers and within the 10–15-km flying range of mosquitos or black flies (such as Simulium). It is assumed that Simulium pruinosum is the vector that precipitates the disease. f) There is a significant number of Fogo Selvagem in family units where multiple, genetically related individuals are affected. Some of these "familial" cases may have localized Fogo Selvagem and low titers of pemphigus autoantibodies, whereas others may develop generalized disease and high titers of autoantibodies. Based on these observations, individuals from families displaying multiple cases of Fogo Selvagem can be separated into three groups, each responding differently to an environmental factor: those who develop extensive, generalized disease and high titers of pemphigus autoantibodies ("high responders"); those with a localized cutaneous disease and low titers of pemphigus autoantiobodies ("low responders"); and normal individuals ("non-responders"). The immunogenetics of Fogo Selvagem is open to future study. g) Finally, autoantibodies against lupus-associated antigens are not present in the sera of patients with Fogo Selvagem.

Clinical examination of the skin, and serologic screening for pemphigus autoantibodies are two specific parameters that may enhance the possibilities of identification of etiologic agents precipitating autoantibody formation and leading to autoimmune disease of the skin. To identify and prove an etiologic agent for this well-characterized autoimmune disease would be of tremendous importance to the understanding of autoimmune skin diseases, and potentially to other organ-specific autoimmune disorders.

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